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■

IN VITRO DIAGNOSTIC PRODUCTS FOR HUMAN USE

Labeling Requirements and Procedures for Development

Title 21—Food and Drugs

CHAPTER I—FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

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PART 167—IN VITRO DIAGNOSTIC PRODUCTS FOR HUMAN USE

Labeling Requirements and Procedures for Development of Standards for In Vitro Diagnostic Products for Human Use

In the FEDERAL REGISTER on August 17, 1972 (37 FR 16613) a proposal was published to establish procedures to develop standards for in vitro diagnostic products. Interested persons were invited to submit comments on the proposal within 60 days. A total of 47 responses was received. These included comments from manufacturer associations, user associations, manufacturers of diagnostic systems, and comments from a consulting firm and an individual consumer. The Diagnostic Products Advisory Committee has met and has provided significant assistance to the agency in the development of this program. At their first meeting the committee considered broad scientific questions concerning the proposed approach and also commented on the question of priorities for the establishment of product class standards. These sources have provided useful information for the development of reasonable regulations governing the manufacture, labeling and performance of in vitro diagnostic products. The comments and conclusions of the Commissioner of Food and Drugs, based on his evaluation, are summarized as follows:

1. A number of comments state that the proposed order purports to be authorized by sections 201, 501, 502, 505, 508, 510, or 701 of the Federal Food, Drug, and Cosmetic Act, and none of these sections explicitly authorizes the promulgation of in vitro diagnostic product standards that constitute substantive rules. Comments were made that the act contains no provision conferring authority on the Food and Drug Administration to determine the new-drug/old-drug status of a product. It was also stated that the FDA does not have authority to make substantive determinations of adulteration or misbranding, and it was claimed that the fact that a product does not conform to an applicable standard does not cause the product to be misbranded or adulterated without regard to the adulteration or misbranding provisions in the act. The question of the authority of the FDA to promulgate regulations of this nature was previously raised and discussed in connection with establishing procedures for classification of over-the-counter drugs, published in the FEDERAL REGISTER of May 11, 1972 (37 FR 9464), and the conclusions reached there are equally applicable here. The standards to be established under these procedural regulations, if upheld by the courts, will prescribe the conditions which an in vitro diagnostic product must meet if it is not to be in violation of the misbranding and/or adulteration and/or new-drug provisions of the act.

2. In response to other comments, the definition of "product class" has been amended to permit the development of product class standards for products with common or related characteristics or those intended for common or related uses in addition to those for use for a particular determination or related group of determinations.

3. Several comments stated that the Federal Food, Drug, and Cosmetic Act does not provide authority for lot-by-lot certification. The Commissioner concludes that such certification is authorized only where it is necessary to assure compliance with the act, and the regulations have been revised to clarify this point. Such certification, where required, may be conducted by the FDA, by the Center for Disease Control, by independent laboratories, or by other organizations, as designated in the standard.

4. Some of the comments objected to the handling of in vitro diagnostic products as a class, without any attempt to classify them as drugs or devices. It is the position of the FDA that as a matter of law it has the authority administratively to determine whether products are drugs or devices; it has made clear its position that until new device legislation is enacted and where the authority inherent in section 505 of the Federal Food, Drug, and Cosmetic Act is necessary to protect the public health, products will be regarded and classified as drugs under the Act. The FDA believes it is not in the public interest to spend time determining which in vitro diagnostic products are drugs and which are devices for the purposes of this regulation. Such a determination will be made only when necessary to bring violative products into compliance.

5. Some comments stated that the FDA has no authority to impose the requirements of the Federal Hazardous Substances Act (FHSA) on in vitro diagnostic products, whether or not they are intended or packaged for use in the household. The regulations do not impose the requirements of the FHSA. The requirement of appropriate warnings is based upon section 502 of the Federal Food, Drug, and Cosmetic Act. The warnings prescribed in 21 CFR Part 191 are appropriate in many cases for in vitro diagnostic products and therefore are incorporated by reference.

6. The section of the proposal dealing with labeling drew the largest number of comments. Several substantive objections to the wording of this section have been accommodated, and several items have been restated for clarification. Many firms commented that specific items were not applicable to certain products; the regulation has been changed to allow flexibility and to permit omissions where certain items of information are inapplicable. The requirement for a fixed format and order for presentation of labeling information has been retained in the interest of uniformity.

7. There was objection to the requirement of a declaration of the quantity or proportion of each reactive, catalytic or inactive ingredient in the labeling accompanying each product. These objections were based primarily on the position that such declaration would disclose valuable trade secrets and proprietary information. The FDA concludes, based in part on its evaluation of these comments and in part on the advice of the Diagnostic Products Advisory Committee, that there is no demonstrated need, as a general requirement, for a declaration of the quantity or proportion of each catalytic or inactive ingredient in the labeling accompanying these products. Such requirements may be determined to be necessary for a particular product or class of products as part of specific product class standards in the future. Therefore, this subparagraph has been amended to require the declaration of the established name (common or usual name), if any, and the quantity or proportion only of each reactive ingredient, unless a standard requires otherwise. Except where such provision is contained in a standard, a general statement indicating the presence of, and characterizing, any catalytic or nonreactive ingredients will be sufficient.

8. A significant number of respondents objected to § 167.2(a)(3) (21 CFR 167.2) stating that information including the quantity or proportion of reactive ingredients is not necessary for the user of these products and that the quantitative description of the reactive ingredients on the label would constitute disclosure of trade secrets. It is the position of the FDA, after consultation with its Advisory Committee, that knowledge of this information is important as a part of adequate directions for use of these products. Therefore, no change has been made in this provision.

9. A large number of comments stated that the requirement that the label bear a statement that the product is intended for in vitro diagnostic use only is unduly restrictive since many of these products are legitimately used for other purposes. This section has been revised to eliminate the word "only". There is nothing in this language that would preclude the use of the product for other legitimate purposes.

10. Several comments indicated concern with the requirement of a statement of the declaration of net quantity or contents in metric terms. This provision has been revised to state a preference, instead of a requirement, for this terminology.

11. Several respondents perceived and stated that the requirement for a lot or control number on the label of products did not reflect an appreciation of the distinct problems associated with multiple-unit products or instruments. This provision as reworded provides for this distinction.

12. The provision relating to exceptions to requirements for certain information on immediate container labels was the subject of many comments. After discussion with the Diagnostic Products Advisory Committee, § 167.2(a)(10)(i)

has been revised to allow the omission of the information on the intended use of the product, proportion of reactive ingredients, warnings, storage conditions, and net contents, required by § 167.2(a) (2), (3), (4), (5), and (7), from the immediate container label under certain specified conditions.

13. A large number of persons objected to the statement in § 167.2(b)(3) that if the product labeling refers to any other procedure, the appropriate literature citations shall be included, and the labeling shall explain the reason for and nature of any differences from the original and their effect on the results, on the basis that this represented comparative labeling. There is no requirement for comparison of one product with another in the regulation as proposed or as finalized. If a manufacturer does make such a comparison, however, it is incumbent upon him to justify it fully in his labeling. The requirement for an explanation of the reason for the change from an original procedure has been deleted, since little benefit would accrue to the intended user of these products from the possession of this information.

14. There were numerous comments received concerning the requirement under §§ 167.2(b)(7)(i) and 167.3(c)(12) (21 CFR 167.2 and 167.3) that any statement on "special preparation of the patient" involved an intrusion into the practice of medicine. The FDA does not believe that this provision represents an intrusion into the practice of medicine, but rather is required for adequate directions for use of the product. To further clarify the intent of these two subparagraphs they have been revised to indicate that such special preparation is needed as it bears on the validity of the test.

15. The same basic objection was raised with respect to the provisions in §§ 167.2(b)(10) and 167.3(c)(15) which requested a statement that additional tests may be required in certain instances. An example of the application of this provision would be to indicate the availability of a confirmatory procedure if the product in question is intended for use as a screening determination. This requirement has been retained since it appears necessary that the user be provided adequate information concerning limitations of the procedure.

16. Other comments requested exclusion of products intended for research and investigational use. The Advisory Committee also made recommendations concerning exceptions from the labeling requirements when diagnostic products are shipped for investigational purposes. The FDA recognizes that adequate information to fulfill the requirements of § 167.2 (a) and (b) may not be available at the time of the earliest testing. It is agreed that a provision to cover the labeling of products prior to commercial marketing is appropriate, and § 167.2(c) has been added to cover this matter. Notification prior to the time of commercial marketing will be required in order to assist the agency in planning its activities and anticipating the needs for the development of product class standards. The agency does not wish to place burdensome requirements upon researchers or other investigators. A simple form for providing such notification will be developed with the advice of the Advisory Committee and other interested persons and made available at a later date. An additional use for the information provided in this notification procedure is to inform field unit of the agency concerning the legitimacy of products shipped with less than full labeling and to minimize the possibility of the unnecessary initiation of compliance activities for products prior to marketing. When commercial marketing is begun, notification to this effect will be required as provided in the procedures for implementation of the Drug Listing Act.

17. Several comments were addressed to the problem of including general purpose laboratory reagents and other multiple-purpose materials in the requirement of 21 CFR Part 167. The Commissioner recognizes that there are hundreds of common laboratory reagents and equipment (e.g., hydrochloric acid and glass beakers), the use of which is generally known by persons trained in their use in laboratory procedures. The inclusion in their labeling of all of the information required by § 167.2 (a) and (b) is not feasible or necessary for the proper use of these general purpose laboratory articles. Therefore, the Commissioner has added a new § 167.2(d) to the regulations to identify the information which must be included in the labeling for those products. New § 167.2(d) is applicable to general purpose laboratory reagents and equipment which may also be used as part of an in vitro diagnostic procedure.

18. Many comments expressed a need for a time period within which to develop and effect the necessary labeling changes in order to avoid imposing an undue hardship on the affected industry. Considering that these regulations require labeling revisions for all products and the development of data in many cases, a period of 12 months from the date of publication of this document will be allowed for compliance with the general labeling requirements of § 167.2 (a) and (b) for all products. Since the problems of labeling for products subject to the requirements of § 167.2(c) are of a lesser magnitude, 6 months from the date of publication will be allowed for compliance.

19. A significant number of respondents objected to the requirement for the disclosure of the complete product formulation in the submission of data to establish a standard. This paralleled the objections to the disclosure of certain formula information in product labeling. The FDA requires information of this kind to establish standards. Quantitative formulae are recognized as valuable trade secrets and are protected from public disclosure by the FDA under the confidentiality statutes governing information obtained by the government.

20. Many respondents objected to the requirement of a specification of the degree of skill, education, and training needed by the "analyst". This section has been reworded. The intention of this requirement is to describe the minimum qualifications for the user of the product. This information is necessary for the agency to develop product class standards appropriate for the intended user.

21. The Diagnostic Products Advisory Committee noted that the provisions for the submission of information under § 167.3(c) might impose an unnecessary burden on an interested person who wished to provide comment more limited than that called for in § 167.3(c). The Commissioner agrees that a more informal submission should be acceptable and the regulation is revised accordingly.

22. In response to comments that the proposed usual period of 60 days for submission of information pertaining to a product standard requested under § 167.3(c) was inadequate, this requirement has been revised to allow a usual period of 90 days for these submissions. However, this will vary for individual product class standards. In view of the notice given in the August 17, 1972, proposal that the first request for information would be for those products used in the determination of glucose, the time for submission of this information will be 60 days.

23. Several comments objected to the provision that after a standard is promulgated or amended the FDA will make data available to the public within 30 days unless the submitter of the data can show that the data are confidential. The applicable statutes (18 U.S.C. 1905; 21 U.S.C. 331(j)) provide for the confidentiality of trade secrets obtained from a person. The FDA is bound by these statutes and will treat as confidential all information that has been demonstrated by the submitter as falling within the confidentiality provisions of one or more of those statutes. Information not exempt from disclosure under the Freedom of Information Act (5 U.S.C. 552 (b)) may not be withheld from public disclosure. Section 167.4 (21 CFR 167.4) of the regulation has been revised to clarify the position of the FDA with respect to the confidentiality of submitted information.

24. Among the product groups considered by the Diagnostic Products Advisory Committee to be of the highest priority for developing product class standards were microbiological antigens, antibodies, and adjuncts; transport and growth media; products for the measurement of immunoglobulins; calibration, reference, and quality control materials; laboratory water; clinical chemistry products used in the determination of glucose, calcium, bilirubin, enzymes, sodium, potassium, chloride, urea, uric acid, cholesterol, and triglycerides; and products used in the determination of hemoglobins. Further deliberation will be required in order to refine and designate or delineate product classes and to place them in appropriate order according to priorities for develop-

ing and establishing product class standards.

25. These regulations do not preclude the imposition of additional requirements under the Act when the Commissioner concludes that such requirements are necessary to protect the public health.

26. Since the provisions of Part 167 apply to those products subject to the exemption from the labeling requirements of section 502(f)(1) of the Act in § 1.106(j), the Commissioner is revising § 1.106(j) to indicate that in vitro diagnostic products subject to that section which are in compliance with the provisions of Part 167 will be deemed to meet the labeling requirements of § 502(f)(1).

27. The provisions of these regulations, including both the requirements for labeling and development of standards, apply to all in vitro diagnostic products, including biologics. All questions concerning in vitro diagnostic products, except for biologicals subject to an existing license under section 351 of the Public Health Service Act, should be addressed to the Diagnostic Products Staff, Bureau of Drugs, BD–207.

Existing licenses for biological products issued under section 351 of the Public Health Service Act will remain in effect until applicable standards are promulgated pursuant to Part 167. For in vitro diagnostic products which are biologics but which have not previously been licensed, compliance with the requirements of Part 167 shall be deemed to constitute compliance with section 351. Such unlicensed products need obtain a license under section 351 only if the Commissioner determines and so informs the manufacturer or distributor pursuant to § 167.6 that a license under section 351 is required in order to protect the public health.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 201, 501, 502, 505, 508, 510, 701, 52 Stat. 1040–1042, as amended, 1049–1051, as amended, 1053, as amended, 1055, as amended, 1056, as amended; 21 U.S.C. 321, 351, 352, 355, 358, 560, 571) and the Public Health Service Act (sec. 351, 58 Stat. 702, as amended; 42 U.S.C. 262) and under authority delegated to the Commission (21 CFR 2.120), Chapter 1 is amended in Part 1 by revising § 1.106(j) and by adding a new Part 167, as follows:

1. In Part 1 by revising § 1.106(j) to read as follows:

§ 1.106 Drugs and devices; directions for use.

* * * * *

(j) *Exemption for in vitro diagnostic products.* A product intended for use in the diagnosis of disease and which is an in vitro diagnostic product as defined in § 167.1(a) of this chapter shall be deemed to be in compliance with the requirements of this section and section 502(f)(1) of the act if it meets the requirements of Part 167 of this chapter.

* * * * *

2. By adding a new Part 167, In Vitro Diagnostic Products For Human Use, to Subchapter C as follows:

Subpart A—Procedural Regulations

Sec.
- 167.1 Definitions.
- 167.2 Labeling for in vitro diagnostic products.
- 167.3 Procedure for establishing, amending or repealing standards.
- 167.4 Confidentiality of submitted information.
- 167.5 Court appeal.
- 167.6 Regulatory action.
- 167.7 General requirements for manufacturers and producers of in vitro diagnostic products.

AUTHORITY: Secs. 201, 501, 502, 505, 508, 510, 701, 52 Stat. 1040–1042, as amended, 1049–1051, as amended, 1053, as amended, 1055, as amended, 1056, as amended; 21 U.S.C. 321, 351, 352, 355, 358, 360, 371.

§ 167.1 Definitions.

(a) "In vitro diagnostic products" are those reagents, instruments and systems intended for use in the diagnosis of disease or in the determination of the state of health in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation and examination of specimens taken from the human body. These products are drugs or devices as defined in section 201(g) and 201(h), respectively, of the Federal Food, Drug, and Cosmetic Act (the act) or are a combination of drugs and devices, and may also be a biological product subject to section 351 of the Public Health Service Act.

(b) A "product class" is all those products intended for use for a particular determination or for a related group of determinations or products with common or related characteristics or those intended for common or related uses. A class may be further divided into subclasses when appropriate.

(c) A "product class standard" is a statement describing performance requirements necessary to assure accuracy and reliability of results, specific labeling requirements necessary for the proper use of a particular class, and procedures for testing the product to assure its satisfactory performance.

(d) "Act" means the Federal Food, Drug, and Cosmetic Act.

§ 167.2 Labeling for in vitro diagnostic products.

(a) The label for an in vitro diagnostic product shall state the following information, except where such information is not applicable, or as otherwise specified in a standard for a particular product class. Section 201(k) of the act provides that "a requirement made by or under authority of this act that any word, statement, or other information appear on the label shall not be considered to be complied with unless such word, statement, or other information also appears on the outside container or wrapper, if any there be, of the retail package of such article, or is easily legible through the outside container or wrapper."

(1) The proprietary name and established name (common or usual name), if any.

(2) The intended use or uses of the product.

(3) For a reagent, a declaration of the established name (common or usual name), if any, and quantity, proportion or concentration of each reactive ingredient; and for a reagent derived from biological material, the source and a measure of its activity. The quantity, proportion, concentration or activity shall be stated in the system generally used and recognized by the intended user (e.g., metric, international units, etc.).

(4) A statement of warnings or precautions for users as established in the regulations contained in Part 191 of this chapter and any other warnings appropriate to the hazard presented by the product; and a statement "For In Vitro Diagnostic Use" and any other limiting statements appropriate to the intended use of the product.

(5) For a reagent, appropriate storage instructions adequate to protect the stability of the product. When applicable, these instructions shall include such information as conditions of temperature, light, humidity, and other pertinent factors. For products requiring manipulation, such as reconstitution and/or mixing before use, appropriate storage instructions shall be provided for the reconstituted or mixed product which is to be stored in the original container. The basis for such instructions shall be determined by reliable, meaningful, and specific test methods such as those described in § 133.13 of this chapter.

(6) For a reagent, a means by which the user may be assured that the product meets appropriate standards of identity, strength, quality and purity at the time of use. This shall be provided, both for the product as provided and for any resultant reconstituted or mixed product, by including on the label one or more of the following:

(i) An expiration date based upon the stated storage instructions.

(ii) A statement of an observable indication of an alteration of the product (e.g., turbidity, color change, precipitate) beyond its appropriate standards.

(iii) Instructions for a simple method by which the user can reasonably determine that the product meets its appropriate standards.

(7) For a reagent, a declaration of the net quantity of contents, expressed in terms of weight or volume, numerical count, or any combination of these or other terms which accurately reflect the contents of the package. The use of metric designations is encouraged, wherever appropriate. If more than a single determination my be performed using the product, any statement of the number of tests shall be consistent with instructions for use and amount of material provided.

(8) Name and place of business of manufacturer, packer, or distributor.

(9) A lot or control number, identified as such, from which it is possible to determine the complete manufacturing history of the product.

(i) If it is a multiple unit product, the lot or control number shall permit tracing the identity of the individual units.

(ii) For an instrument, the lot or control number shall permit tracing the identity of all functional subassemblies.

(iii) For multiple unit products which require the use of included units together as a system, all units should bear the same lot or control number, if appropriate, or other suitable uniform identification should be used.

(10) Except that for items in paragraph (a) (1) through (9) of this section: (i) In the case of immediate containers too small or otherwise unable to accommodate a label with sufficient space to bear all such information and which are packaged within an outer container from which they are removed for use, the information required by paragraph (a) (2), (3), (4), (5), (6) (ii) (iii) and (7) of this section may appear in the outer container labeling only.

(ii) In any case in which the presence of this information on the immediate container will interfere with the test, the information may appear on the outside container or wrapper rather than on the immediate container label.

(b) Labeling accompanying each product (e.g., a package insert) shall state in one place the following information in the format and order specified below, except where such information is not applicable, or as specified in a standard for a particular product class. The labeling for a multiple-purpose instrument used for diagnostic purposes, and not committed to specific diagnostic procedures or systems, may bear only the information indicated in paragraph (b) (1), (2), (6), (14), and (15) of this section. The labeling for a reagent intended for use as a replacement in a diagnostic system may be limited to that information necessary to identify the reagent adequately and to describe its proper use in the system.

(1) The proprietary name and established name (common or usual name), if any.

(2) The intended use or uses of the product and the type of procedure (e.g., qualitative or quantitive).

(3) Summary and explanation of the test. Include a short history of the methodology, with pertinent references and a balanced statement of the special merits and limitations of this method or product. If the product labeling refers to any other procedure, appropriate literature citations shall be included and the labeling shall explain the nature of any differences from the original and their effect on the results.

(4) The chemical, physical, physiological, or biological principles of the procedure. Explain concisely, with chemical reactions and techniques involved, if applicable.

(5) Reagents. (i) A declaration of the established name (common or usual name), if any, and quantity, proportion or concentration or each reactive ingredient; and for biological material, the source and a measure of its activity. The quantity, proportion, concentration or activity shall be stated in the system generally used and recognized by the intended user (e.g., metric, international units, etc.). A statement indicating the presence of and characterizing any catalytic or nonreactive ingredients (e.g., buffers, preservatives, stabilizers).

(ii) A statement of warnings or precautions for users as established in the regulations contained in Part 191 of this chapter and any other warnings appropriate to the hazard presented by the product; and a statement "For In Vitro Diagnostic Use" and any other limiting statements appropriate to the intended use of the product.

(iii) Adequate instructions for reconstitution, mixing, dilution, etc.

(iv) Appropriate storage instructions adequate to protect the stability of the product. When applicable, these instructions shall include such information as conditions of temperature, light, humidity, and other pertinent factors. For products requiring manipulation, such as reconstitution and/or mixing before use, appropriate storage instructions shall be provided for the reconstituted or mixed product. The basis for such instructions shall be determined by reliable, meaningful, and specific test methods such as those described in § 133.13 of this chapter.

(v) A statement of any purification or treatment required for use.

(vi) Physical, biological, or chemical indications of instability or deterioration.

(6) Instruments: (i) Use or function.

(ii) Installation procedures and special requirements.

(iii) Principles of operation.

(iv) Performance characteristics and specifications.

(v) Operating instructions.

(vi) Calibration procedures including materials and/or equipment to be used.

(vii) Operational precautions and limitations.

(viii) Hazards.

(ix) Service and maintenance information.

(7) Specimen collection and preparation for analysis, including a description of: (i) Special precautions regarding specimen collection including special preparation of the patient as it bears on the validity of the test.

(ii) Additives, preservatives, etc., necessary to maintain the integrity of the specimen.

(iii) Known interfering substances.

(iv) Recommended storage, handling or shipping instructions for the protection and maintenance of stability of the specimen.

(8) Procedure: A step-by-step outline of recommended procedures from reception of the specimen to obtaining results. List any points that may be useful in improving precision and accuracy. (i) A list of all materials provided (e.g., reagents, instruments and equipment) with instructions for their use.

(ii) A list of all materials required but not provided: Include such details as sizes, numbers, types, and quality.

(iii) A description of the amounts of reagents necessary, times required for specific steps, proper temperatures, wavelengths, etc.

(iv) A statement describing the stability of the final reaction material to be measured and the time within which it shall be measured to assure accurate results.

(v) Details of calibration: Identify reference material. Describe preparation of reference sample(s), use of blanks, preparation of the standard curve, etc. The description of the range of calibration should include the highest and the lowest values measureable by the procedure.

(vi) Details of kinds of quality control procedures and materials required. If there is need for both positive and negative controls, this should be stated. State what are considered satisfactory limits of performance.

(9) Results: Explain the procedure for calculating the value of the unknown. Give an explanation for each component of the formula used for the calculation of the unknown. Include a sample calculation, step-by-step, explaining the answer. The values shall be expressed to the appropriate number of significant figures. If the test provides other than quantitative results, provide an adequate description of expected results.

(10) Limitation of the procedure: Include a statement of limitations of the procedure. State known extrinsic factors or interfering substances affecting results. If further testing, either more specific or more sensitive, is indicated in all cases where certain results are obtained, the need for the additional test shall be stated.

(11) Expected values: State the range(s) of expected values as obtained with the product from studies of various populations. Indicate how the range(s) was established and identify the population(s) on which it was established.

(12) Specific performance characteristics: Include, as appropriate, information describing such things as accuracy, precision, specificity, and sensitivity. These shall be related to a generally accepted method using biological specimens from normal and abnormal populations. Include a statement summarizing the data upon which the specific performance characteristics are based.

(13) Bibliography: Include pertinent references keyed to the test.

(14) Name and place of business of manufacturer, packer, or distributor.

(15) Date of issuance of the last revision of the labeling identified as such.

(c) A shipment or other delivery of an in vitro diagnostic product shall be exempt from the requirements of paragraphs (a) and (b) of this section and from a standard promulgated pursuant to this part provided the following conditions are met:

(1) For a product in the laboratory research phase of development, and not represented as an effective in vitro diagnostic product, all labeling bears the statement, prominently placed: "For Research Use Only. Not for use in diagnostic procedures."

(2) For a product being shipped or delivered for product testing prior to full commercial marketing (e.g., for use on

specimens derived from humans to compare the usefulness of the product with other products or procedures which are in current use or recognized as useful), all labeling bears the statement, prominently placed: "For Investigational Use Only. The performance characteristics of this product have not been established."

(3) The person making a shipment or delivery under paragraph (c)(2) of this section shall submit to the FDA a notification that such shipments are being made.

(4) Within 30 days after the first commercial shipment of an in vitro diagnostic product, the person making such shipment shall submit the information required by the Drug Listing Act as provided in § 132.5 of this chapter.

(d) The labeling of general purpose laboratory reagents (e.g., hydrochloric acid) and equipment (e.g., test tubes and pipettes) whose uses are generally known by persons trained in their use need not bear the directions for use required by § 167.2 (a) and (b), if their labeling meets the requirements of this paragraph.

(1) The label of a reagent shall bear the following information:

(i) The proprietary name and established name (common or usual name), if any, of the reagent.

(ii) A declaration of the established name (common or usual name), if any, and quantity, proportion or concentration of the reagent ingredient (e.g., hydrochloric acid: Formula weight 36.46, assay 37.9 percent, specific gravity 1.192 at 60° F.); and for a reagent derived from biological material, the source and where applicable a measure of its activity. The quantity, proportion, concentration or activity shall be stated in the system generally used and recognized by the intended user (e.g., metric, international units, etc.).

(iii) A statement of the purity and quality of the reagent, including a quantitative declaration of any impurities present. The requirement for this information may be met by a statement of conformity with a generally recognized and generally available standard which contains the same information (e.g., those established by the American Chemical Society, U.S. Pharmacopeia, National Formulary, National Research Council).

(iv) A statement of warnings or precautions for users as established in the regulations contained in Part 191 of this chapter and any other warnings appropriate to the hazard presented by the product; and a statement "For Laboratory Use."

(v) Appropriate storage instructions adequate to protect the stability of the product. When applicable, these instructions shall include such information as conditions of temperature, light, humidity, and other pertinent factors. The basis for such information shall be determined by reliable, meaningful, and specific test methods such as those described in § 133.13 of this chapter.

(vi) A declaration of the net quantity of contents, expressed in terms of weight or volume, numerical count, or any combination of these or other terms which accurately reflect the contents of the package. The use of metric designations is encouraged, wherever appropriate.

(vii) Name and place of business of manufacturer, packer, or distributor.

(viii) A lot or control number, identified as such, from which it is possible to determine the complete manufacturing history of the product.

(ix) In the case of immediate containers too small or otherwise unable to accommodate a label with sufficient space to bear all such information, and which are packaged within an outer container from which they are removed for use, the information required by paragraphs (b)(2), (b)(3), (b)(4), (b)(5), and (b)(7) of this section may appear in the outer container labeling only.

(2) The label of general purpose laboratory equipment (e.g., a beaker or a pipette) shall bear a statement adequately describing the product, its composition, and physical characteristics if necessary for its proper use.

§ 167.3 Procedure for establishing, amending or repealing standards.

(a) *Basis for standards and available approaches to developing standards.* Whenever in the judgment of the Commissioner the establishment of a product class standard is necessary to reduce or eliminate unreasonable risk of illness or injury associated with exposure to or use of an in vitro diagnostic product and there are no other more practicable means to protect the public from such risk, he may propose such a standard. In proposing a product class standard he shall consider, and publish in the FEDERAL REGISTER findings on, the degree of risk or injury associated with the use of the product, the availability of information relating to the sciences upon which the products or their uses are based, the approximate number of products subject to the standard, the medical need for the products, and the probable effect of the standard upon the utility, cost, or availability of the product, and available means of achieving the objective of the standard with a minimal disruption of supply and of reasonable manufacturing and other commercial practices. Three procedures are available for developing product class standards and may be proposed on the initiative of the Commissioner or by petition of interested persons: (1) An existing standard may be utilized, (2) interested persons outside of the Food and Drug Administration may develop a proposed standard or (3) the Food and Drug Administration may develop the standard. If a petition is filed by an interested person, it shall be in the form prescribed in § 2.65 of this chapter with the number of copies specified therein.

(b) *Advisory committee.* An advisory committee of qualified experts shall be appointed to advise the Food and Drug Administration on the priorities for establishing product class standards, the scientific basis for in vitro diagnostic products, the selection of reference methodologies and reference materials, the adequacy and reasonableness of proposed standards and other related matters as determined by the Commissioner.

(c) *Request for information and comment.* Whenever a new standard is to be developed, the Commissioner will publish a notice in the FEDERAL REGISTER requesting the submission of all information, data, and views relevant to a specific product class for review and evaluation. Any interested person may submit comments and views on any matter relevant to the development of the standard, including the factors required by paragraph (a) of this section, to be considered by the Commissioner. The format for such submission may be determined by the nature of the information to be submitted. Any product performance information submitted shall relate to the performance of that product as marketed or intended for marketing. For information submitted by a manufacturer of a product which will be affected by the standard, the specific product information requested and the format for submission shall be as described below unless changed in the FEDERAL REGISTER notice. The time allotted for submission will ordinarily be 90 days. Four copies of the information and data on any product within the designated class shall be submitted, indexed, and bound.

(1) Name of product class and date of FEDERAL REGISTER statement.

(2) Proprietary name of product.

(3) Name of person responsible for submission.

(4) Intended use or uses of the product.

(5) A statement categorizing the procedure (e.g., qualitative or quantitative).

(6) Copies of label and all other labeling under which product is currently marketed or, for a proposed product, the label and all other labeling under which marketing is intended.

(7) Description of the product, as appropriate: For example, if the product is or includes a reagent, state the proprietary name and established name (common or usual name), if any, and quantity, proportion, or concentration of each reactive, catalytic, or inactive ingredient. If the product is a biological material, list the source and a measure of its activity. Include a statement of any purification or treatment required for use. If the product is or includes an instrument or equipment, describe as appropriate its use or functions, installation procedures and any special requirements, principle of operating instructions, calibration procedures including materials and/or equipment to be used, operation precautions and limitations, hazards, and service and maintenance instructions.

(8) Stability information: A description of, and data derived from, studies of the stability of the product. For any product that requires manipulation (e.g., reconstitution or mixing), stability data shall be described for the reconstituted or mixed product. Describe the means by which the information was developed. The data shall be for the product in the

container in which it is marketed to assure, among other things, that the container is not reactive, additive, or absorptive to an extent that alters the product or its performance. Include any expiration period data which supports any expiration date which appears in the labeling of the product. Describe the storage conditions necessary for the product, such as temperature, light humidity.

(9) Hazards to user: A statement of the principal hazards associated with the product. Include the result of tests conducted to determine the applicability of hazard warnings or cautions, including those established in the regulations contained in Part 191 of this chapter.

(10) History of methodology: A brief history of the methodology, with pertinent references. All references to reports of adverse or unfavorable experience with the product or the procedure on which it is based shall be included. If the product procedure is the same as one which has been published, cite the reference. If the product is based on a modification of a published procedure, cite the reference, state the reason for and the nature of the modification and the effect such modification may have on the results of the procedure as compared to the original. Include data illustrating the comparison of the modified procedure to the original procedure.

(11) Principle of test: An explanation of the test procedure including the chemical, physical, physiological, or biological principle of the procedure with chemical reactions and techniques involved, if applicable.

(12) Specimen collection and preparation: A description of the specimen to be subjected to analysis: (i) Special precautions regarding specimen collections, including special preparation of the patient as it bears on the validity of the test.

(ii) Additives, preservatives, etc., necessary to maintain the integrity of the specimen.

(iii) Known interfering substances and their effect on the procedure and results.

(iv) Appropriate storage, handling or shipping instructions.

(13) Procedure: A detailed, step-by-step description of the test procedure from reception of the specimen to obtaining of results, including any points that may be useful in improving precision and accuracy. Give the exact details of calibration. Identify reference material. Describe preparation of reference sample, use of blanks, etc. Include a description of methods to be used in determining the standard curve.

(14) Results: Explain the procedure for calculating the value of the unknown. Give an explanation of each component of the formula used for the calculation of the unknown. Include a sample calculation, step-by-step, explaining the answer. Values should be expressed to the appropriate number of significant figures. Provide the basis for evaluation of nonquantitative test results.

(15) Limitation of the procedure: Include a statement of the limitations of the procedure and an explanation of extrinsic factors, if any, that may affect the results. Include statements regarding minimum training needed by the user, special precautions, interfering substances, likelihood of obtaining false positive or false negative results, etc. Positive data showing a lack of interference by commonly occurring substances shall be supplied. If a more specific or more sensitive laboratory test is indicated in certain instances, the indication for the additional test shall be stated and data submitted to support its value.

(16) Support of claims: Include all available data, published or unpublished, which supports or is critical of the product or its procedure. Include data for both normal and abnormal subjects and a description of the population or populations studies. State, for each claim: (i) Labeling claim.

(ii) Background documentation: Provide a bibliography and reprints of all pertinent references.

(iii) Procedure used for collecting evidence for claim.

(iv) Description of statistical protocol.

(v) Description of sampling procedure.

(vi) Summary of raw results in tabular form.

(vii) Analysis of results.

(viii) Statement of interpretation of results.

(17) Summary of scientific basis of procedure: A summary of the data and views setting forth the scientific rationale and purpose of the product, and the scientific basis for the conclusion that the product has or has not been proven accurate and reliable for its intended uses. If there is an absence of controlled studies in the material submitted, an explanation as to why such studies are not considered necessary shall be included.

(18) If the submission is by a manufacturer, a statement signed by the person responsible for such submission, that to the best of his knowledge it includes unfavorable information as well as any favorable information, known to him pertinent to an evaluation of the performance of the product. Thus, if any type of scientific data is submitted, a balanced submission of favorable and unfavorable data must be submitted. The same would be true of any other pertinent data or information submitted, such as consumer surveys or marketing results.

(d) *Review and evaluation.* Any existing standard or petition for a product class standard, together with any information and comments submitted pursuant to a published notice, will be reviewed and evaluated by the Food and Drug Administration in consultation with its advisory committee and the Center for Disease Control.

(e) *Proposed product class standard.* When the Commissioner has concluded that the criteria in paragraph (a) of this section are met and the information available has been reviewed and found to justify the establishment of a product class standard, he shall publish in the FEDERAL REGISTER a proposed product class standard establishing conditions under which the products in the class are safe and effective and not adulterated or misbranded. The standard shall include a statement of the performance requirements necessary to assure accuracy and reliability of results, specific labeling requirements for the proper use of the products in the class, and procedures for testing the products to assure satisfactory performance at the time of marketing. The standard may include, where necessary to assure the accuracy and reliability of results, individual lot testing by or at the direction of the Food and Drug Administration, in addition to that normally required of the manufacturer; except that the Commissioner shall exempt any particular product from such a requirement upon a showing that the manufacturer has demonstrated such consistency in the production of that product, in compliance with the regulations, as is adequate to insure the accuracy and reliability of results, and the Commissioner shall revoke the requirement of individual lot testing under the standard when it is no longer necessary to the accuracy and reliability of the results of the product class covered by the standard. Any interested person may, within 60 days after publication of the proposed standard in the FEDERAL REGISTER, file written comments on the proposal, in quintuplicate, with the Hearing Clerk, Department of Health, Education, and Welfare, Room 6–88, 5600 Fishers Lane, Rockville, MD 20852. Comments may be accompanied by a memorandum or brief in support thereof. All comments may be reviewed at the Office of the Hearing Clerk during regular working hours, Monday through Friday.

(f) *Referral to an independent advisory committee.* The Commissioner may, in his discretion, refer a proposal under paragraph (e) of this section to an independent advisory committee of experts qualified in the subject matter at issue, for a report and recommendations with respect to any matter involved in such proposal which involves the exercise of scientific judgment. The Commisioner shall designate the chairman of each panel. The independent advisory committee may consult any person in connection with the matter referred to it. Any interested person may request, in writing, an opportunity to present oral views to the committee. Any interested person may present written data and views which shall be considered by the committee. The full report(s) of the committee and summary minutes of its meetings shall be made available upon request after submission of the report(s) to the Commissioner.

(g) *Final product class standard.* After reviewing all comments received in response to the proposal and considering al available relevant information, the Food and Drug Administration, in consultation with its advisory committee and the Center for Disease Control, and after consideration of any report of an independent advisory committee if the

matter involved has been so referred, will publish in the FEDERAL REGISTER a final order containing a product class standard. This order shall state the reasons for promulgating the product class standard and the date the standard will become effective.

(h) *Petition to amend or repeal standards.* The Commissioner may propose to amend or repeal any standard established pursuant to this procedure or any interested person may petition the Commissioner for such action. A petition shall set forth the action requested and a detailed statement in support of the action. After review of the petition, the Commissioner may deny the petition if he finds a lack of reasonable support or he may publish a proposed amendment of or proposed repeal of the established standard in the FEDERAL REGISTER if adequate support has been presented. The petition shall be in the form specified in § 2.65 of this chapter with the number of copies and other information as specified therein. A new drug application submitted for an in vitro diagnostic product which does not comply with an applicable effective product class standard will be considered as a petition to amend the standard. Petitions for repeal or amendment for which reasonable support has been furnished will be handled pursuant to the procedures established in paragraphs (e)–(g) of this section.

§ 167.4 Confidentiality of submitted information.

(a) Data and information submitted pursuant to the provisions of § 167.3 or § 167.2(c) and falling within the confidentiality provisions of 18 U.S.C. 1905 or 21 U.S.C. 331(j) shall be treated as confidential by the Food and Drug Administration and any consultant to whom it is referred. Confidentiality of information will be determined in accordance with the provisions of Part 4 of this chapter.

(b) Data and information submitted pursuant to § 167.3 in connection with the establishment, amendment or repeal of a product class standard will be made publicly available at the Office of the Hearing Clerk of the Food and Drug Administration 30 days after publication of a proposed product class standard, except for the identity of inactive ingredients, any quality control or other manufacturing data or information, or other data and information to the extent that the person submitting it has demonstrated that it falls wihin the confidentiality provisions of 18 U.S.C. 1905 or 21 U.S.C. 331(j).

§ 167.5 Court appeal.

The product class standard promulgated in the final order represents final agency action from which appeal lies to the courts. The Food and Drug Administration will request consolidation of all appeals in a single court. Upon court appeal, the Commissioner, at his discretion, may stay the effective date for part or all of the standard pending appeal and final court adjudication, and may establish a new effective date after final court adjudication.

§ 167.6 Regulatory action.

Any in vitro diagnostic product is subject to regulatory action if it fails to conform to an applicable product class standard or the general labeling requirements of § 167.2. If the product is a device, it is adulterated in violation of section 501 and it is misbranded in violation of section 502 of the act. If the product is a drug, it is in violation of section 505 as well as sections 501 and 502 of the act. If the product is a biological, it is in violation of sections 501, 502, and 505 of the Federal Food, Drug, and Cosmetic Act and section 351 of the Public Health Service Act. Deviations from an established standard may be justified only by an amendment to the standard. Compliance with this part shall be deemed to constitute compliance with the labeling and new drug requirements of the act and with the labeling and licensing requirements of section 351 of the Public Health Service Act, unless the Commissioner otherwise informs the manufacturer or distributor of an in vitro diagnostic product of additional requirements imposed pursuant to either statute in order to protect the public health.

§ 167.7 General requirements for manufacturers and producers of in vitro diagnostic products.

(a) *Registration and product listing.* Any person who owns or operates any establishment engaged in the manufacture, preparation, compounding, or processing of an in vitro diagnostic product should register such establishment and list such product(s) in accordance with the procedures established under Part 132 of this chapter. Any such establishment not currently registered should register within 30 days of the effective date of this regulation. Any such establishment currently registered as a drug establishment shall at the next period for reregistration use the appropriate registration form indicating that it is a producer of in vitro diagnostic products. Registration forms may be obtained from the Department of Health, Education, and Welfare, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852, or at any Food and Drug Administration district office. Registration and listing do not constitute an admission or agreement or determination that a product is a "drug" within the meaning of section 201(g) of the act.

(b) *Compliance with good manufacturing practices.* In vitro diagnostic products shall be manufactured in accordance with current good manufacturing practices. The principles established in Part 133 of this chapter, "Drugs; Current Good Manufacturing Practice in Manufacturing Processing, Packing, or Holding", should be followed as a guideline.

Effective date. This order shall be effective on March 15, 1973, except that § 167.2 (a), (b), and (d) shall be effective on March 15, 1974, and § 167.2(c) shall be effective on September 17, 1973.

(Secs. 201, 501, 502, 505, 508, 510, 701; 52 Stat. 1040–1042, as amended, 1049–1051, as amended, 1053, as amended, 1055, as amended, 1056, as amended; 21 U.S.C. 321, 351, 352, 355, 358, 360, 371)

Dated: March 12, 1973.

CHARLES C. EDWARDS,
Commissioner of Food and Drugs.

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